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OPINIONS CONCERNING FATIGUE AND MAN'S ADAPTATION TO HEAT

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Chief Medical Officer H. Laborit

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OPINIONS CONCERNING FATIGUE AND MAN'S ADAPTATION TO HEAT

(Results achieved and present-day orientation of research in the Navy)

Chief Medical Officer H. Laborit

ABSTRACT: Experiments aimed at maintaining or restoring normal metabolic functioning of cells in the case of work and fatigue in a hot environment. The following therapeutic suggestions are advanced: 1) An energy and dietetic supply of substances, which has not yet been studied sufficiently, but in which a major role can already be predicted for monosaccharides, vitamins, certain amino acids and ions; 2) The maintenance of a normal splanchnic vasomotor activity capable of preserving a correct hepatorenal functioning and limiting certain disturbances of the nitrogen metabolism; 3) A surveillance of the intestinal flora; 4) A guided replacement of hydro-electrolytic losses; in this connection, hospital clinical practice has recently shown the indispensable separation in the supply of chlorine from that of sodium, as well as the importance of K and Mg; 5) Control measures must rely on certain blood and urine examinations, but special attention should be given to the study of neuro-muscular excitability, in view of its simplicity and the wealth of information which it provides.

We have no intention of returning, in a general survey, to the already numerous articles devoted to man working in arid zones or hot environments. The documentary study made in 1957 by B. Metz and G. Lambert has covered the problem in a simple, clear fashion and furnishes a good bibliography. We could not do better. /217*

We wish only to explain how we were induced to study these problems, for what reasons we have broached them from a rather personal angle, and why we have sought therapeutical approbation (judged by some to be premature) of our working hypotheses. Finally, we will conclude by bringing forward the ideas which are presently guiding our experimental research on animals and man.

On board modern naval units, without port-holes, with electronic gear evolving considerable heat, where means of regulating and controling the

*Numbers in the margin indicate pagination in the foreign text.

environment cannot be obtained except to the detriment of the military efficiency of the ships, life and work are carried out under climatic conditions rather similar, most frequently, to those of either tropical or desert climates. As a naval physician, it was not possible for me to remain indifferent to the problem. On the other hand, as surgeons and revivers, it has been our custom, for very many years, to consider the individual as a psychosomatic entity, reacting as a unit to the environment, whether this be the surgeon, microbes, poisons, the social milieu or a military projectile. This is why we were tempted to take up /218 thermal exposure, work, and what is conventionally called fatigue, in the same way in which we have taken up the different problems confronting us in the past.

This position is not a simple hypothesis. Although we wrote in 1952 that the organism does not react in many ways, that it responds in a similar fashion to various attacks, the facts show that the unconscious life of our vital organs is not capable of developing a defense tatic and strategy, which we have been tempted to detect only because of our incorrigible tendency to ascribe animate characteristics to such a function.

These are the ideas which led, among others, to the introduction of phenothiazines and chlorpromazine in therapeutics. This drug has demonstrated its multiple value and therapeutic effectiveness to traumatic, toxic and infectious shock, as well as to emotional psychoses, which are often nothing but the expression of an inordinate reaction of the individual to his social environments.

The study of organic reactions to various attacks obliges us to consider the human organism as a whole, reacting as an integral unit to variations in environment, but consisting of cellular individuals, citizens of the organic collective, whose combined action is effected by correlation systems. These correlation, liaison systems make it possible for the energy liberated by each cellular element to cooperate harmoniously in the terminal state of the whole, that of the human organism, the essential purpose of which is, we believe, to maintain the motor independence of this organism within its environment.

This is why, for fourteen years, after having studied the normal and pathological functioning of intracellular correlation systems, viz., the vegetative, vasomotor and endocrine, we have been induced in the last four or five years to become interested in the functioning of the elementary unit of the organic society, the cell.

For some years now physiologists have been coming up with the essential information concerning the functioning of the cell element, which they have studied in isolated organs or isolated cells, owing to very refined electrophysiological or biochemical techniques. The original part of our work has been to integrate this cell physiology into organic physiology, which may appear to be premature to some people. It is true that such integration is possible only if, as we proceed from cell to organic physiology, we also have sufficient clinical experience gained from general physiopathology. In other words, experience gained not within the laboratory walls, but which intrudes on a therapeutist as a result of the complex disorders that occur in a human organism subjected to extremely varied types of attacks.

It is perhaps presumptuous to wish to give a sketchy survey of infinitely complex phenomena. We have resolved to do so in complete awareness. /219

a. It is certain that liberation of energy by the cell is accompanied by penetration of Na ions from the ambient medium into the intracellular medium and by evacuation of potassium from the cell. Metabolic processes must then repel the sodium and reintegrate the potassium, reestablishing the difference in ion concentration on each side of the membrane, and thus the membrane potential, called the "rest" potential.

b. The metabolic processes of the cells can be roughly illustrated by saying that enzyme systems extract H^- ions and electrons from substrates and then eject them from the cell by way of oxidizing-reducing systems, which pass them on to oxygen. The cell maintains its intracellular ion concentration by exchanging H^- ions with extracellular K^+ ions.

c. The metabolic processes, by regulating the ion concentration gradients on each side of the cell membrane, thus control the permeability. But the permeability conditions the exchange intensity and therefore the metabolic intensity. Thus, in the physiological state, cell functioning is automatically regulated (Figures 1 and 2).

Organic Physiological Regulation

Let us arbitrarily choose as the effector the extracellular medium (MEC), more precisely, the ratio of concentrations of B HCO_3 and H HCO_3 in this medium ($\frac{B\ HCO_3}{H\ HCO_3}$), and let us take the maintenance of the H^+ ion concentration as the purpose of this effector.

The factor which will cause a positive aerobiotic change in this concentration is cellular liberation of H^+ ions and CO_2. Thus, the preceding sketch (Figure 2) will end up with the "extracellular medium" as effector, and the effect of the cell will become the positive factor of the extracellular medium. The effect chosen for the latter will be its H_2CO_3 concentration (Figure 3). When the latter rises, the cell membrane depolarizes. Thus we find negative feedback in response to this effect, terminating in membrane potential. But we have seen that membrane polarization itself has a negative effect on the metabolic intensity. Minus times minus equals plus. The increase in concentration of H^+ ions, acidosis (provided it remains within physiological limits, /221 within its domain) will increase metabolism: this is positive feedback, and the system will function, but in the transient state. If one or several negative factors do not make it possible for the H_2CO_3 concentration of the extracellular liquids to reach constant equilibrium, the cell organization will soon break down, since we have just seen that such organization can be maintained only under constant conditions. The reason why this is so is that in Figure 2 we have chosen the quantity of liberated H_2CO_3 as the effect exerted by the cell effector, and that in Figure 3 the H_2CO_3 concentration of the extracellular medium as the

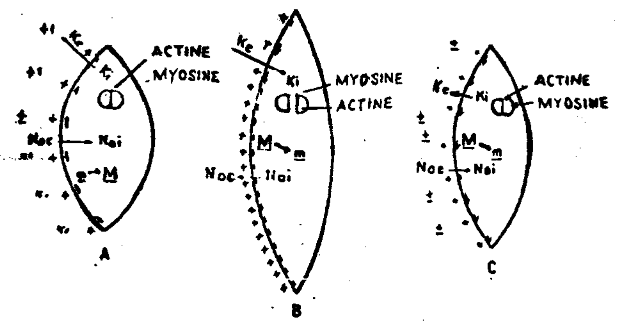

Figure 1. Interpretive Hypothesis Concerning Automatic Cardiac Action.

A—Depolarized Membrane. Ki Output, Nae Input. Actine-Myosine Association. Increased Tonus. Systole. Increased Membrane Permeability. Rise In Metabolism = m → M.
B—Metabolic Increase to Reintegrate the Ke to Ki, Extract the Nae: Hence Membrane Repolarization and Dissociation of the Actine and Myosine. Diastole. But Repolarization → Reduced Exchange → Decrease in Metabolism = M → m.
C—Decrease in Metabolism Permits Depolarization: K Escapes, Na Returns → Cycle Repeats.

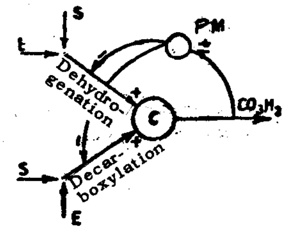

Figure 2.

C—Cell; PM—Membrane Potential; S—Substrates; E—Enzymes.

effect exerted by the MEC effector. We have thus proceeded from the level of the cell to that of the organism.

The negative factors are the lungs and the kidneys, which ensure extra-organic evacuation of the CO_2 and H^- ions. Let us first outline the renal activity, but to simplify this activity we will restrict ourselves to considering only one of the mechanisms for evacuating the H^- ions by this organ (Figure 4a).

We know that owing to the presence of carbonic anhydrase the tubular cell produces H_2CO_3 from CO_2 and plasmatic H_2O. The H_2CO_3 traps the filtered sodium at the glomerule level and forms $NaHCO_3$, which is reintegrated in the organism. Thus one H^- ion is liberated in the urine. This mechanism can be represented as in Figure 4b.

We see that here we are dealing with positive feedback, with a transient operation which will end up with reintegration of CO_2 and Na in the organism in proportion to the number of H^- ions evacuated in the urine. Conversely, the increase in the number of evacuated H^- ions (linked to strong anions) and in the amount of retained CO_2 and Na will be proportional to the increase in plasmatic concentration of CO_2 and Na. The mechanism can be limited only by

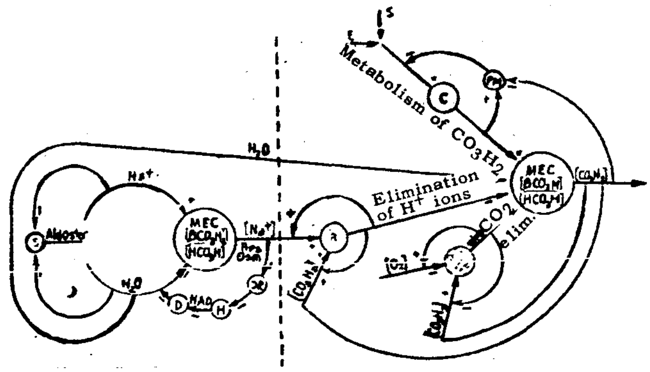

Figure 3.

S—Suprarenal Glands. MEC—Extracellular Medium. OR—Osmoreceptors. H—Hypophysis. D—Diuresis. HAD—Antidiuretic Hormone. R—Kidney. Ventil—Ventilation. ChR—Chemoreceptors. CR—Respiratory Center. Press. Osm.—Osmotic Pressure. C—Cell. PM—Membrane Potential. Aldoster.—Aldosterone.

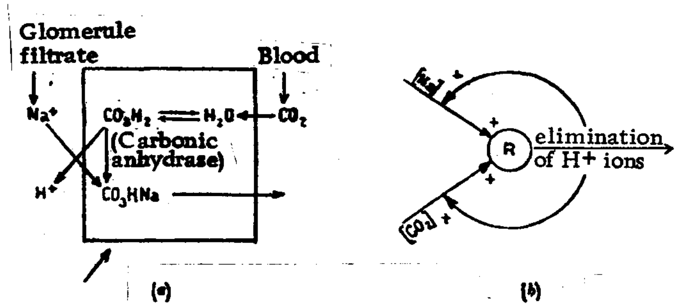

Figure 4.

a parallel reduction of the H⁻ ion concentration. We will see later in this article from several examples that this scheme is verified by the facts and explains them.

Note that the quantity of water retained is proportional to the quantity of Na retained. There is interaction between two factors which act on the MEC effector, because the more water that is retained, the more the H_2CO_3 concentration of the extracellular liquids decreases and consequently the more the concentration of CO_2 and Na decreases. Therefore we must add a third negative factor to regulation of the H_2CO_3 concentration of the extracellular liquids, namely, extracellular water. We will examine how it is regulated later on.

Insofar as the lungs are concerned (Figure 5), we can consider the effector to be ventilation; this is controled by the respiratory centers (CR), which are particularly sensitive to the CO_2 concentration in the blood [CO_2], and by the chemoreceptors (ChR), which are particularly sensitive to the O_2 concentration [O_2] (Figure 4). The higher the O_2 concentration, the more the chemoreceptors are inhibited, and this is a negative factor for ventilation. On the contrary, the greater the increase in CO_2 concentration, the more the respiratory centers are excited (physiologically, that is, when the variable factors remain within certain limits, within their domain). This is a positive factor in ventilation. When ventilation is very active, more CO_2 is evacuated, and there is less CO_2 /222 in the blood; in other words, negative feedback in response to a positive factor, steady work which keeps the effect in equilibrium. Likewise, when negative feedback is more effective, oxygenation is better; this is positive feedback, but in response to the negative ventilation factor, and therefore here too we have continuous work.

It can be seen therefore (Figure 3) that equilibrium in H_2CO_3 concentration of the extracellular liquids can also be summarized as the maintenance of equilibrium between the cellular production of H_2CO_3 (positive factor) on the one hand and kidney evacuation of H^- ions and lung evacuation of CO_2 (negative factors) on the other hand. The water content, combined with that of Na, and therefore of CO_2, is also a negative factor of the H_2CO_3 concentrations.

Now let us take the Na^+[Na^+] concentration as an effect of the extracellular medium, which is the same as the osmotic pressure (the left-hand part of Figure 3), provided we neglect for the time being the other determinant elements of this pressure. This concentration of Na^+ will have a positive factor, the quantity of Na^+ in the extracellular medium, and a negative factor, the quantity of water present in the same medium. It is assumed that the total value of these two factors depends on the secretion of aldosterone by the suprarenals. In fact, the latter controls how much water and Na^+ are retained. But such retention inhibits secretion of aldosterone, that is, we have negative feedback and steady work, which may cause the volume-receptors to intervene, a point still to be discussed.

But the osmotic pressure [Na^+] has a negative effect on the osmoreceptors; since they have been excited by dilution. These osmoreceptors act on the occipital lobe of the hypophysis, which they inhibit; once again, a negative effect. The hypophysis secrets an antidiuretic hormone (HAD) which also affects diuresis negatively, and the latter in turn acts negatively on the quantity of water present in the extracellular medium. Thus we have positive feedback in response to a negative factor and continuous functioning of osmotic pressure [Na^+].

Now let us join the two diagrams. This can be done by using the osmotic pressure in this figure (3) (since we have considered it to be identical to [Na^+]) as a factor at the level of the tubular renal cell which eliminates H^+ ions, causing the negative H_2O factor on the right-hand side of the figure to appear and also the H_2O factor on the left-hand side.

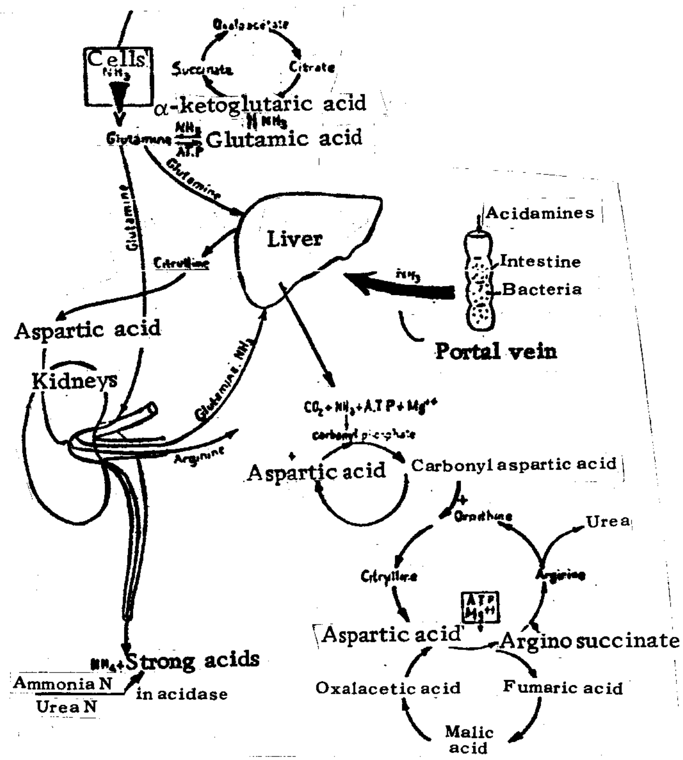

Figure 5.

Physiopathological State

It is immediately evident that all living physiological phenomena can be reduced to transformation within the cells of hydrogen molecules bound to substrates which are supplied by food intake into H^+ ions and electrons accepted by the oxygen. The latter are transported to the emunctories, which excrete them. Another point must be noted, that is, that transport of hydrogen through the organism terminates in relative economy of the "bases," in particular of Na^+ and water, since the more H^- ions excreted by the kidney the more Na^+ and water retained by it. By this very fact, however, greater secretion of aldosterone is dampened. Consequently, quantitative hydrosaline homeostastis will be reestablished.

For an effect to be produced it is necessary for the value of the factors to remain within certain limits, within a domain. This is the case in physiology, in which, because of hysteresis, the reaction is fluctuating, but remains harmonious. /224 But the value of these factors depends on the environment, and it is evident that conservation of the physiological state is possible only within certain narrow limits of environmental variation.

These limits also vary with training, which must not be confused with adaptation. In our opinion, training permits a living organism to broaden the limits within which its homeostatic equilibrium can be maintained, whereas adaptation is a new state of equilibrium resulting from some biological rearrangement, more or less profound, in which homeostatic regulation again becomes possible.

Thus, in view of the disorders occupying our attention, variations in the environmental characteristics go beyond the limits within which homeostasis can be maintained if a new state of equilibrium, characteristic of adaptation, is not reached.

But then even if adaptation is achieved, maintenance of the new homeostatic equilibrium is generally rendered difficult by the very fact that the enviornmental characteristics are at the limit of the adaptive possibilities of the organism supporting them.

This is the reason, in our opinion, for the fundamental interest inherent in the notion of recuperative rate, that is, the rate at which the rest state and state of cellular and organic equilibrium are reestablished after some interruption has perturbed the cellular and organic equilibrium. It is evident that more rapid and more perfect recuperation will prevent chronic fatigue from having the chance to set in as a result of a repeated perturbation.

Now that we have presented these general ideas, let us see what the probable feedback mechanisms are, so that we will know how to limit their harmfulness.

At the Cell Stage

As we have seen, in the physiological state, i.e., metabolic functioning, the Na^+ pump ensures that this ion is ejected after intracellular penetration and simultaneously that the K^+ is reintegrated. In the physiopathological state, however, these metabolic processes are not sufficient to ensure restorative exchange of the cations, and this is why the cell is enriched with sodium and impoverished of potassium. This is also the reason why there is a considerable /225 expenditure of carbohydrates, required because of metabolic increase, an appreciable fraction of which is anaerobic. Anaerobic glycolysis is very costly, since the Pasteur effect is suppressed.

At the Organic Stage

1°. The first group of facts should demonstrate the case when the effort does not exceed the limits of homeostatic regulation.

Metabolic enhancement results in increased cell liberation of H_2CO_3 as long as the aerobic phenomena remain predominant. Cardiac and lung regulation (tachycardia and polypnea) are rapid, renal regulation less so, but the buffer systems reduce the delay in effectiveness and temporarily maintain the pH. In addition, diuresis is increased and sodium retention is not apparent.

2°. But if the intensity and duration of enrivonmental variations are such that the result is a splanchnic vasomotor reaction, metabolic acidosis sets in.

In effect:

a. The muscle contracts under anaerobic conditions, only recuperation being aerobic, resulting in glycolysis and liberation of organic acids, such as pyruvic and lactic;

b. The supply of carbohydrates runs the risk of being insufficient; and in any case protein-lipid catabolism results not only in the liberation of organic acids more dissociated than H_2CO_3, but also of NH_3. The toxic effect of the latter on the nervous system is indisputable, but its primary effect is to accelerate oxidizing cycles in order to get rid of the glutamic acid and glutamine by means of α-ketoglutarie acid (Bessmann). Such acceleration results itself in an increase in protein-lipid catabolism, aggravating acidosis;

c. Finally, and above all, vasoconstriction in the splanchnic area results in hepatorenal and intestinal hypoxia. The kidney is no longer able, by excreting strong acids, to eliminate the H^+ ions (bound to ammonia which it gets from the glutamine) in the form of ammonium salts. The acidosis will be aggravated, being now regulated only by the ventilation system and the buffer systems. It is in danger of failing to compensate. In general physiopathology we believe that this mechanism can be upheld as being real because of the hyperammoniemia which we have found in different types of attacks, in particular, in the case of fatigue driven to exhaustion in the swimming test with rats (Laborit et al.).

The balance existing between excretion of NH_3 in the form of ammonia salts in the case of acidosis, or its integration in the cycle of the ornithine and of the urea at the liver stage, expressed by Maillard's coefficient, becomes impossible, since the functioning of these two organs is perturbed.

Everything takes place as if the preferential supply required by the brain, lungs, heart and muscles for the accomplishment of work or the maintenance of motor independence in the midst of the environment occurs at the expense of organs located in the abdomen and momentarily not necessary for its realization. /226

An important fact should be noted. During the course of recuperation, it can be assumed that the return to a normal renal vascularization will result in the excretion of urine with a very high acid and ammonia content. The chloride content of the blood will drop sharply. On the other hand, since H^+ ions are exchanged with Na^+ ions at the level of renal tubes, if the organism is relatively little depleted in Na^+ it risks being depleted considerably in Cl^- ions.

A similar mechanism must no doubt also be considered in regard to thermal attack and profuse sweating. Thus, both on the clinical level and in the subject with which we are concerned, we must draw an absolute distinction between the fate and the different role of Cl^- and Na^+ and we must not talk about a salt deficiency or a saline therapy. In our opinion, uremias allegedly due to a lack of salt are uremias primarily due to a lack of sugar and then to a lack of Cl^-. We would be capable of providing several convincing clinical examples of this fact. And, in all such cases, the ionogram which explores only the extracellular medium, although it is significant with respect to Cl^-, has absolutely no significance for cations whose extra- or intracellular location cannot be determined precisely.

In any case, the functioning of the liver probably assumes a considerable importance, which has been almost ignored up to the present time, in the struggle against aggresive effects of the environment and in recuperation. The metabolism of NH_3 is the central concept for studying the functioning of the digestive tract and the role of its flora (intestinal NH_3), nitrogen catabolism (deaminations), the functioning of the liver (ureogenesis) and of the kidneys (elimination of strong acids in the form of ammonium salts). If the study of pH variations provides us with information on the value of organic control mechanisms, ammoniemia will yield information on the functioning of cells and of the splanchnic system. The ultimate goal is the maintenance or the return to an efficient, self-regulated cellular functioning (Figures 5 and 6).

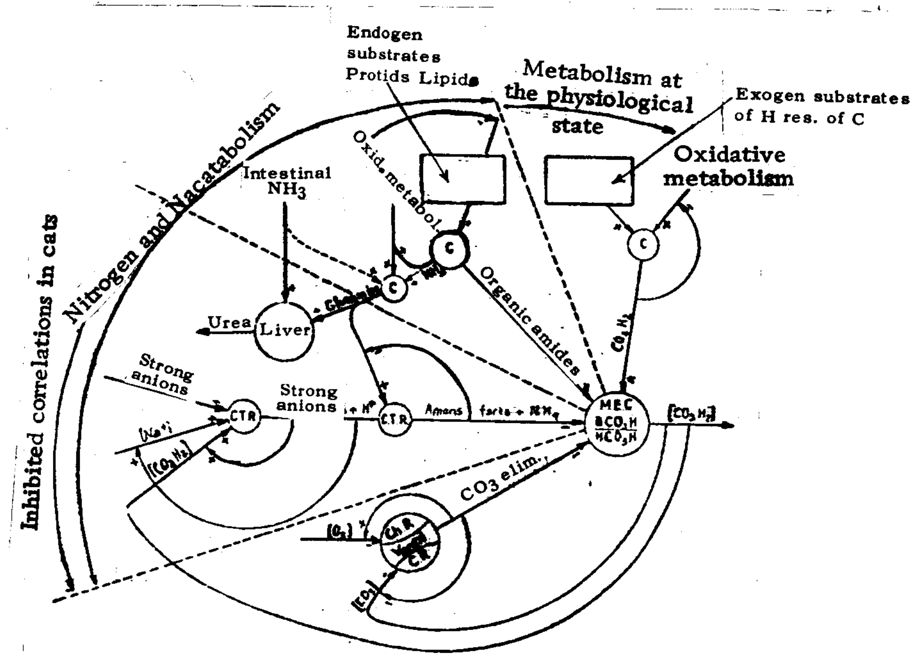

Figure 6.

MEC) Extracellular medium; CTR) Tubular renal cell; C) Cell; ChR) Chemoreceptors; CR) Respiratory centers.

Whereas in clinical practice it is conceivable that the restorer of life (treating physician) can maintain homeostasis in a dictatorial manner by prohibiting splanchnic vasoconstriction, a factor essential for shock if this condition is prolonged, the maintenance of motor independence with respect to the environment requires in a man at work that circulatory readjustments be preserved.

Through a better knowledge of the modalities of this motor independence, our role will be to limit any evil (ill-fated) consequences of this condition.

Study of Fatigue and Heat Reactions

The term "fatigue" is an indefinite term. In man, psychic factors play a considerable role in the establishment of this subjective state. For this reason we have used for experimental purposes the rat swimming test carried out to the point of exhaustion resulting in drowning without an intervention in extremis. The development of this technique required several months. The technique requires a certain amount of practice and is only of value when based on statistical results.

This test is no longer valid for the study of heat effects. Many months were required in addition to develop a test which can be carried out in a heat environment whose different characteristics can be varied (wheel, moving staircase).

Experimentally, we have evaluated the quality (degree) of recuperation by subjecting our test animals to a second test performed 2 1/2 hours after the first one. The duration of this second test, up to the point where exhaustion is reached, allows a judgment of the animal's recuperation faculties and of the efficiency of prophylactic therapeutics (preventive treatment).

When we began our experiments, we decided to study separately those two factors before studying them together, and we started by studying the effect of work extending to the point customarily known as exhaustion; we then planned to study the effects of thermal shock (heat exposure), and finally the combination of both work and thermal shock.

A. Animal Experiments

a. We varied the sodium concentration of the extracellular medium both above and below its normal value, knowing the important effect exerted by the extracellular sodium concentration on the energy functioning and on the metabolism of the nerve and muscle studied in an isolated organ.

Sodium deficiency facilitates the onset of exhaustion but also makes recuperation (recovery) more easy. On the other hand, we only studied the effect of NaCl. Since we have just called attention to the necessity of avoiding a confusion between the role played by Na^+ and Cl^-, it would no doubt be useful to vary the content of these two ions separately, since Cl^- and Na^+ not only play a cellular role but also and particularly an organic role through their different intervention in maintaining the extracellular pH. We must repeat again that the organism is faced essentially with the problem of eliminating the H^+ ions, which is generally achieved by means of saving Na^+ ions.

b. We have enriched the intracellular medium with potassium, and this has improved the performances obtained in both the first and second tests, and thus has made recuperation (recovery) more easy. The same applies, but less clearly, to magnesium and calcium.

c. We then attempted to influence the metabolic processes by supplying various vitamins, cytochrome C, and coenzyme A. Only ATP (adenosine triphosphate), as inexplicable as its therapeutic efficiency may be, yielded significant results.

d. We have also used certain substrates, such as glucose, glutamic acid, and aspartic acid. /230

Finally, it is the combination of the two salts, the potassium and magnesium salts of aspartic acid, which gave the best results.

e. Then, in a long study extending over more than 2 years, we attempted to study the effect of these salts on rats, rabbits, and dogs before undertaking a study on humans. We cannot even think of presenting here a general review of the work done by our group on this subject. We shall limit ourselves to the statement that, in our opinion, the action of aspartic acid consists essentially in facilitating the introduction of CO_2 and NH_3 into the hepatic cycle of ornithine and urea and in improving the hepatic and cellular functions which this acid provides; of course, we must take into account the interesting factor of the potassium and magnesium supplied by the salts of aspartic acid.

Under the influence of this acid, the total CO_2 content in the plasma is reduced without a drop in pH, ammoniemia drops sharply, the injected NH_4Cl is detoxicated, and the nitrogen catabolism is reduced (reduction of urea and ammonia nitrogen both in blood and in urine).

B. Human Experiments

The study conducted by G. Laborit and A. Kind on their pre-operational hospitalized patients has confirmed the facts established in animals on the biological plane.

However, in order to evaluate its effect on human fatigue, we had to consider at first which types of tests could furnish the most valuable results. After what we have said concerning physio-biological equilibria such as we understood them, it is easy to see that we should devote our main attention to the pH and to the acid reaction (R. A.), both in humans and in animals.

1. Unfortunately, control of the pH is a relatively delicate measure which cannot be applied at present within the framework of human work. However, it will perhaps be possible for us to achieve this goal soon under sufficient security conditions.

2. The more easy comparative study of R. A. and of the chloride content of blood and urine can hopefully provide us with interesting information on the acid-base equilibrium.

3. The investigation of variations in the blood mass, ionograms and research on urinary electrolyte losses, which are the only tests capable of supplying precise information on the fate of ions, are also difficult to realize at places of work.

The same applies to nitrogen balances, and we are now considering methods for carrying out such tests. We have recently undertaken the task of measuring ammoniemia. It is too early yet to determine the interest of such a measurement in this specific research task. /231

4. Finally, we are faced with physiological tests, namely:

(a). Those concerned with the cardiac rhythm (Flask's test, Lian's test). Experience has shown that such tests are sometimes useful in studying chronic fatigue but are discouraging in studying acute fatigue in young and healthy men.

(b). But, particularly, the study which we have been carrying out for 5 years on the neuromuscular excitability using the Pluven and Guiot rheotome and the facts discovered by us on hospitalized patients concerning the variations of this excitability as a function of ionic membrane exchange and of metabolic disturbances controlled by the balance method; these facts have permitted us to achieve a simple reestablishment of hydrogen ion equilibrium in our patients before, during and after operation and have led us to study the neuromuscular excitability during fatigue, following the work done by Moynier and Guiot. This study was carried out on hospitalized patients, on athlete of the Joinville batallion together with Thiebault, and more recently on divers of the Navy Combat Group at Toulon and on ship crews. This study appears to us at the present time to be the most reliable and sensitive test of global physio-biological disturbances, which otherwise take a long time and are difficult to estimate.

Subjective sensations, performances and neuro-muscular activity allow us to believe that salts of aspartic acid play an important role in the struggle against fatigue and in human recuperation, thereby confirming the results obtained in animal experiments. Several hundred test subjects in which these salts have been used for 2 years provided us with satisfactory and sometimes surprising results. However, it is out of the question to treat fatigue only with a single means and we shall explain later in this article how we believe experiments should be carried out on an ensemble (set) of prophylactic and curing measures.

I. Heat Exposure

Without going into a detailed account of the physiopathology of this type of attack, we can summarize the reaction which it generates in the organism by stating that it consists essentially in a readjustment of the cardiovascular system and of circulating fluids resulting in a preferential irrigation of cutaneous zones capable of losing heat by evaporation.

The circulatory readjustments comprise cutaneous vasodilatation and the acceleration of the cardiac rhythm.

A. In the acute period, prior to onset of acclimatization, this leads to the following results:

a. The increase in the capacity of the circulatory system cannot be readjusted rapidly enough by drawing upon water present in tissues, inasmuch as the dehydration following sweating makes it more difficult to maintain the circulating fluid mass. This is the explanation given by Robinson, Turrel, Belding and Howarth for the conditions of vertigo, tachycardia, and collapse encountered sometimes. /232

b. It is conceivable that the mechanisms of splanchnic anoxia noted above presumably assume all their value in this hypothesis and will be aggravated by muscular exertion. Oliguresis and a reduced hepatic circulation are certainly present. We know their consequences: acidosis, disruption of the permeability of the digestive tract walls, toxic and ammonia resorptions which the liver is incapable of rendering innocuous, and considerable glycolysis. Oliguresis uses cations sparingly but prohibits the elimination of NH_3 which the liver is probably incapable of converting to any great extent into urea. We do not know the amount of ammonia eliminated with perspiration nor the variations of ammoniemia during the course of heat exposure. It is those facts, a knowledge of which is important, that we intend to investigate.

B. Following our observations, hemo-concentration resulting from water losses and sodium retention must trigger the release of the antidiuretic hormone, on the one hand, and the secretion of aldosterone, on the other, which will help it to ensure separately the reestablishment of the osmotic equilibrium and of the volumetric equilibrium of the bulk of extracellular fluids. This is what constitutes adaptation, which will be realized when the circulating mass will be volumetrically adapted to its new repartition and the increased capacity of the circulating system. Thus a new homeostatic equilibrium will be achieved, capable of oscillating harmoniously by reacting to the new characteristics of the environment.

Recuperation remains, however, the dominant problem both during the acute period and when adaptation will be achieved. The studies of Robinson, Turrel, Belding and Howarth (1953), cited by Metz and Lambert, confirm the hypothesis which was the starting point of our therapeutic orientation towards fatigue, since these authors have recorded a loss of K in cells during heat exposure and have noted the reappearance of this cation in cells during recuperation. Metz and Lambert have also disclosed a negative potassium balance in such cases.

Discussion

What thoughts do the facts which we have just rapidly summarized suggest?

1. First, we believe that a distinction must be drawn between NaCl losses in sweat and the NaCl losses normally observed in urine. In the physiological

state, indeed, there is an equilibrium between the nutritional intake and the urinary excretion of NaCl.

When the organism must struggle against acidosis, the opposite takes place, since sodium retention and increased chloride elimination are observed. /233

Finally, in the physio-pathological state, this dissociation between sodium and chloride urinary excretion appears only during the recuperation period, when renal circulation returns to normal. Thus, in the case of heat exposure, we believe that it is absolutely not certain that the recuperation period must be accompanied by a supplementary intake (supply) of NaCl, since Na will be retained and Cl will be eliminated in the urine. Therefore, the logical result of several days of such a therapeutic treatment would be an excess amount of sodium, which can certainly be considered as harmful on the basis of the clinical experience available to us.

On the other hand, it appears logical to achieve a supplementary intake (supply) of chlorides, which we shall willingly associate with cations such as K^+ and Mg^{++}, and perhaps Ca^{++}. The latter two cations offer the advantage of supplying two Cl^- ions for each cation. Thus, we believe that Cl^-, the metabolic role of which appears to be extremely limited, is only used to excrete H^+ ions as a result of its transit in the extracellular medium from the digestive tract to the urinary tract. If our opinion is correct, Cl^- would appear to perform the same role as oxygen does in the kidneys.

2. Until proof of the contrary, we do not think that it is logical to carry out an endocrine treatment, except for a proven case of endocrine deficiency. It is known indeed that cortical suprarenal hormones not only retain water and Na^+ in the organism, but also direct their intracellular penetration and the escape of K^+ from cells, thus representing an ionic exchange process which we must attempt to oppose.

3. Facilitate recuperation.

Indeed, no matter what efforts are made to diminish the painful character of the environment, the essential problem in our opinion is to ensure the best possible recuperation. The preceding thoughts are already aimed at this goal.

We believe that to achieve this goal, it would be useful, in every organized collective system, to plan the creation of a recuperation (recovery) hall in which climatic conditions (temperature, hygrometry, ventilation) will be studied in order to allow, for a given climate, the most rapid recuperation. After completion of their work, subjects would come to this hall to submit themselves to certain therapeutic rules; the following rules can be proposed as part of a non-limiting enumeration:

(a). Short sessions of hyperventilation teaching the subject to ventilate by using his diaphragm, an indispensable element for the rapid elimination of CO, thus favoring oxygenation, a light hypocapnic alkalosis. It is known that the latter promotes the elimination of Na^+ ions at the kidney level [Laborit, Favre and Delacroix (1965)] and that it also promotes the reintegration of K^+ ions in cells. /234
It is itself an element of thermal control (or regulation).

(b). Hydration with highly sugared fluids containing aspartic acid salts which, as was shown by us, exert a favorable effect on hepatic and cellular functions, on ammonia detoxification, and on neuro-muscular fatigue (neuro-muscular excitability curves). This hydration would compensate losses due to perspiration and hyperventilation. Glucose and ATP would provide the cellular energy nutrition indispensable to cellular repolarization. The reduction of the extracellular sodium concentration due to hydration would compensate the sodium retention accompanying the renewal of diuresis.

(c). Ionic supply, already initiated by the potassium and magnesium salts of aspartic acid. Magnesium will facilitate urinary sodium excretion. Potassium will compensate the loss of this ion in the urine. We have already explained why the supply of chlorides is necessary. Finally, the absorption of small doses of neuroplegic compounds or tranquillizers will promote splanchnic vasodilatation, cellular reintegration of K^+, restoration of the rest potential, reduction of the muscular tonus and, by facilitating sleep, reducing anxiety and decreasing psychic tension, will help to achieve a peripheral and central relaxation.

Baths and massage treatments will also be included in this program.

Finally, prior to starting work, consumption of a meal rich in NaCl will permit achieving a maximum liberation of energy at the time an effort is exerted, while the use of NaCl should be prohibited during the evening meals.

Before we reach a conclusion and not wanting to be accused of any absolute finality, we believe that it might be useful to recall the control of Cl, mineral ions and carbohydrates in some foods and we have extracted the corresponding figures from already classical tabulations (see Table).

A stricking factor is the high content of Cl and K^+, and the low content of Na, in foods currently used in desert countries, as compared to the often reverse proportions of these elements present in foods frequently consumed in temperate or cold regions.

Conclusion

The several ideas which we have propounded in this article and which must be defined more precisely on the basis of animal experiments that have already been initiated can be summarized by stating that they are directed to the maintenance or rapid restoration of a normal metabolic functioning at the cellular level. For this purpose, therapeutics offers the following suggestions:

a. An energy and dietetic supply of substances, which has not yet been studied sufficiently, but in which a major role can already be predicted for monosaccharides, vitamins, certain amino acids and ions.

b. The maintenance of a normal splanchnic vasomotor activity capable of preserving a correct hepatorenal functioning and limiting certain disturbances of the nitrogen metabolism.

	Cl	Na	K	Ca	Mz	Carbo-hydrate
	mg, %	mg, %	mg, %	mg, %	mg, %	mg, %
Fresh bananas	125	0.5	420	8	31	21
Dried dates	283	0.9	790	65	65	75
Dried figs	105	34	780	162	72	73
Watercress	109	—	301	187	28	3.7
Fresh coconuts	122	39	363	20	39	12.8
Dried coconuts	125	53	693	43	77	53.2
Whole wheat	177	—	334	38	122	71.8
Cornflour	146	0.6	213	10	84	78
White bread	621	446	109	30	30	52
Molasses	501	43	1,238	273	81	60
Butter	330	220	14	16	1	0.4
Parmesan cheese	1,350	880	131	1,220	42	2
Fresh milk	106	51	143	118	12	9.94
Whole eggs	120	81	100	54	13	0.7
Raw egg yolk	124	26	100	147	16	0.7
Raw egg white	161	110	100	20	11	1

c. A surveillance of the intestinal flora.

d. A guided replacement of hydro-electrolytic losses; in this connection, hospital clinical practice has recently shown the indispensable separation in the supply of chlorine from that of sodium, as well as the importance of K and Mg.

e. Control measures must rely on certain blood and urine examinations, but special attention should be given to the study of neuro-muscular excitability, in view of its simplicity and the wealth of information which it provides.

Our sole purpose in this study, which includes a much larger number of hypotheses than established facts, was to show how we plan to continue our studies of work and fatigue in a hot environment, by integrating physiopathology and this treatment in a much more general framework designated by us as the study of aggressive effects ("aggressology").

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